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10/599,401	02/27/2007	Seth Hallstrom	16785.10	8352

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,401	HALLSTROM ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-18 are pending.

The preliminary amendment filed 2/27/07 which amends claims 1-7, and adds claims 8-18 has been entered.

Foreign Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Austria on 3/29/04. It is noted, however, that applicant has not filed a certified copy of the Austria 556/2004 application as required by 35 U.S.C. 119(b).

IDS

The references cited in the IDS filed 9/27/06 have been considered by Examiner except the reference (citation No.2) because this reference is not in English nor translated; and thus, it has been lined through.

Election/Restrictions

Applicants' election filed 8/17/09 of Group II, claims 1-18 (a method of the treatment), and elect ischemia disorder (from claim 1) and protein S-nitroso albumin (from claims 3 and 8) for examination without traverse is acknowledged. Applicants also elect (species election) "reduced glutathione" for examination. Claims 1-18 which are drawn to a method of manufacturing a pharmaceutical preparation and the elected "ischemia", "S-nitroso albumin" and "reduced glutathione" are under examination.

Objection to specification

The disclosure is objected to because of the following informalities:

(1) The specification is objected to becasue lacks the section of "Brief description of drawings".

(2) At page 3, line 10, "SH-group" should be spelled out in full for the fist instance of use. Also, see page 11, line 10, "RS-NO" and line 15, "HAS" set forth in the term "S-NO-HAS"; and page 13, line 15, "GSH".

(3) At page 3, lines 13 and 14, the meaning "molecular weight of at most 10.000" is unclear because molecular weight of thiol group (see line 13) is larger than 10 daltons. Similar correction should be made in the "abstract". Also, at page 3, line 14, ' *„thiol group "* ' should be changed to "thiol groups".

(4) At page 3, line 11, "pharmaceutical combined preparation" should be changed to "pharmaceutically combined preparation"; similar change should be made throughout the specification.

(5) At page 7, line 6, "NO_{2-}" and "NO_{-}" should be changed to "NO_2^-" and "NO^-", respectively.

(6) At page 12, line 11, "$(kg)^{1,01}$" and "$(kg)^{1,26}$" should be clarified; what is the meaning of "-1,01" and "-0,26"; are they refer to "-1.01" and "-0.26", respective

Objection to claims

Claims 1-18 are objected to because claim 1 recite non-election invention, i.e., non-elected the method of manufacturing a pharmaceutical combined preparation comprising a protein which thiol groups are nitrosated. Also, claim 1 is as containing non-elected subject matters, i.e., disorder states other than the elected "ischemia" set forth in claim 1.

In claim 3, before "nitrosated SH-groups" should add "said" or "the". Also, claim 3 is objected because of containing the no-elected subject matters "S-nitroso orosomucoid, S-nitroso plasminogen activator, S-nitroso fibrinogen, S-nitroso Lys-plasminogen and S-nitrosohaemoglobin".

Claim 4 is objected because of containing the no-elected subject matters "-cysteine….dihydrolipoic acid and the oxidized form thereof" as set forth in the claim.

In claim 6, "wherein a compound" should be changed to "wherein the compound" for clarity. In addition, claim 6 is objected to as containing the non-elected subject matters: "L-cysteine, L-cysteinyl glycine, γ-glutamyl cysteine and dihydrolipoic acid".

In claim 7, "wherein a therapeutic protein" should be changed to "wherein the therapeutic protein' for clarity.

Claim 8 is objected to as containing non-elected subject matters "S-nitroso albumin, S-nitroso orosomucoid, S-nitroso plasminogen activator, S-nitroso fibrinogen, S-nitroso Lys-plasminogen and S-nitrosohaemoglobin".

Claim 9 is objected to as containing non-elected subject matters "L-cysteine, N-acetyl cysteine, L-cysteinyl glycine, γ-glutamyl cysteine, penicillamine, penicillamide, N-acetyl penicillamine, N-acetyl penicillamide, homocysteine, captopril, dihydrolipoic acid and the

oxidized formed thereof". Also, in claim 9, "a compound" should be changed to "the (said) compound".

Claim 13 is objected to as containing non-elected subject matters "L-cysteine, N-acetyl cysteine, L-cysteinyl glycine, γ-glutamyl cysteine and dihydrolipoic acid".

In claims 14 and 15, "wherein a therapeutic protein" should be changed to "wherein the therapeutic protein" for clarity. Additionally, in claims 14 and 15, "a therapeutic protein" should be changed to "the (said) therapeutic protein". Similarly, see also claims 16-18.

Objection to the drawings

The drawings (filed 9/27/06) of Figure 1e, 2a, 2b, 3a are 3b are objected to because the title and brief description of each figure belong to the section "Brief description of the drawings" which should be separately set forth in the specification. Also, in Figure 4, the label of the horizontal axes of Figure 4a, 4b and 4c is unclear; the arrow with "min" beneath the figure is vaguely presented.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The

objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recited "…and having an average molecular weight"; the recitation is not apparent whether or not it refers to the "therapeutic protein" (recited at line 1 of the claim 1) and/or refers to the "compound" (recited at line 2 of claim 1). Claims 2-18 which depend from claim 1are also rejected. Claim 1 is directed to a method (a "use claim" [see above 101 rejection]) lacking the method step(s), which renders the claim indefinite.

Claim 2 does not make it clear whether or not the thiol group(s) in the "protein" and/or "compound" set forth in claim 1 is/are nitrosated.

Claim 3 recites "*at least one of S-nitroso albumin ...S-nitroso haemoglobin is contained as the therapeutic protein*"; the recitation is unclear whether or not (i) the "therapeutic protein" comprises other amino acid sequence(s) in addition to amino acid sequence(s) of the "S-nitro albumin" or/and haemoglobin, or/and (ii) the "therapeutic protein" is a fusion protein comprising the "S-nitro albumin" or/and "S-nitro haemoglobin" thereof, or/and (iii the "therapeutic protein" contains all of the S-nitroso proteins (e.g., albumin and haemoglobin) set forth in the claim. Suggest "wherein the therapeutic protein is selected from the group consisting of *S-nitroso albumin ...*". Similarly, see also claim 4 recitation "*at least one of reduced glutathione ...is/and contained as the compound*".

Claim 7 recitation "N, O, C-nitrosation" is unclear because it ambiguously refers to (i) "N-introsation", (ii) "O-introsation" or (iii) "C-introsation" individually, or refers to any combination of (i), (ii) and/or (iii) thereof. Similarly, see also claims 14-18.

Claim 8 lack antecedent basis for "S-nitroso albumin" (elected and thus examined) because claim 2 from which claim 8 depends does not recite said "s-nitroso albumin".

Claim 9 lacks antecedent basis for "reduced glutathione" (elected and thus examined) because claim 2 from which claim 9 depends does not recite said "reduced". In addition, claim 9 is indefinite in "*reduced glutathione .... and the oxidized form thereof is reduced*" because only oxidized (not the "r*educed*" form) of glutathione can be chemically reduced.

Claim 10 lacks antecedent basis for "wherein S-nitroso albumin" because neither claim 1 nor claim 4 from which claim 10 depends sets forth the "S-nitroso albumin".

Claim 11 lacks antecedent basis for "reduced glutathione" because neither claim 8 nor claims 1 or 2 from which claim 11 depends sets forth the "reduced albumin".

Claim 12 lacks antecedent basis for "wherein S-nitroso albumin" because neither claim 9 nor claims 1 or 2 from which claim 12 depends sets forth the "S-nitroso albumin".

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlag et al. (US Pat. No. 6358918 B1) in view of Tsikas et al. (*Biochem. Biophys. Acta* (2001) 1546, 422-434) and Hallstrom et al. (2002) *Circulation*, 105, 3032-3038).

In patent claims 16-18 and 21, Schlag et al, teach a method of treating ischemia comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one thiol nitrosated (i.e., S-nitroso) thiol-group-containing proteins, wherein "at least one" encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent

claims 21) and low-molecular weight protein, e.g., glutathione (col.2, lines 61 and 62), as applied to instant claims 1, 3, 5 and 8-12.

At least 95% of the thiol-group-containing proteins are S-nitrosated (patent claim 19) while N-nitrosation, O-nitrosation and/or C-nitrosation level is less than 10% (patent claim 24). This meets the limitation of instant claims 2, 7 and 14-18.

The glutathione has free thiol group (col. 2, lines 52-54, 61 and 62) indicating the said glutathione is a reduced form of glutathione, as applied to instant claims 4 and 5.

The glutathione occurs in human blood (col. 1, lines 48-56), as applied to instant claims 6 and 13.

Schlag et al. do not expressly disclose or provide working example for combined use of S-nitroso-albumin and S-nitroso-glutathione (GSH) for the treatment discussed above.

Yet, Schlag et al. et al. teach the higher S-nitrosation level for the higher the "NO-coupled effect" when administered (col. 2, lines 23-34), even near complete S-nitrosation of albumin is preferred, e.g., > 95% S-nitroso albumin (see patent claims 17, 19 and 21). And, Schlag et al. et al. teach medical applications, e.g., treating cerebral ischemia, using such nitrosated pharmaceutical preparation (see col.6, lines 56-60 and 63).

Tsikas et al. teach that S-transnitrosylation of albumin by S-nitroso-glutathione (GSNO) is the most favored and most efficient mechanism for producing the S-nitroso albumin (SNOALB) in vivo and in vitro (see abstract and page 423, left col., lines 19, "formula (1)", and right col., lines 17-21). The teachings of Schlag and Tsikas are applicable to claim 1 and dependent claims therefrom.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use S-nitroso albumin and S-nitroso GSH together for treating disorder such as ischemia. This is because Schlag et al. have taught that the higher S-nitrosation level of albumin is proportional to the higher the "NO-coupled effect". Said effect refers to that NO gradually released by S-nitroso albumin (or S-NO-HAS) actively scavenges superoxide (O_2^-) wherein O_2^- would cause injury to blood vessel endothelium, i.e., ischemia (see page 3033, left col., lines 1, 5-9, 16 and 17, and page 3032, right col., lines 3-5 and 10-14, Hallstrom et al.). The S-nitroso albumin treatment of skeletal muscle against ischemia/reperfusion (I/R) is a powerful tool in reducing the I/R state (see page 3038, last paragraph, Hallstrom et al.). The best way to achieve /maintain high level of S-nitrosation of albumin for said I/R treatment would be addition of the S-nitroso GSH with the S-nitroso albumin, since the S-nitroso GSH assisted S-transnitrosylation of albumin is the most favored and most efficient mechanism for formation of the S-nitroso albumin, as taught by Tsikas et al. (see above). Upon reading the Schlag, Tsikas and Hallstrom references, one of ordinary skill in the art would have recognized importance and benefit of inclusion of the S-nitroso GSH in the treatment of ischemia by the S-nitroso albumin. Thereby, one of ordinary skill in the art would have formulated the S-nitroso GSH and S-nitroso albumin together, and would have tried to use said formulation for treating ischemia with reasonable expectation of success. Therefore, combination of the references' teachings renders the claimed invention *prima facie* obvious in the absence of unexpected result.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The

examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
September 13, 2009